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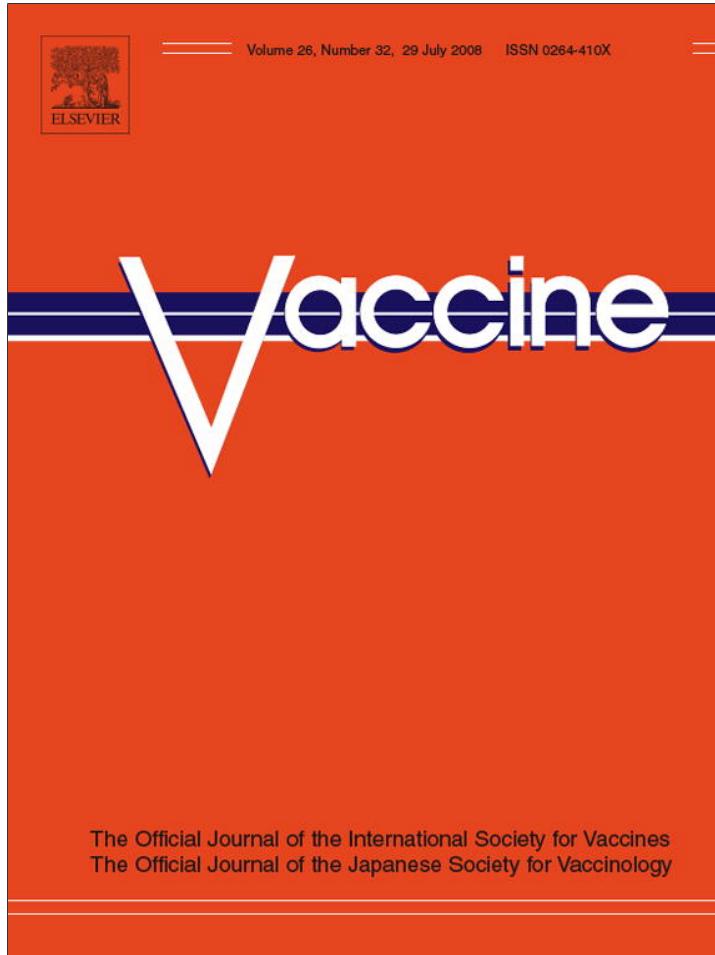
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US military service members vaccinated against smallpox in 2003 and 2004 experience a slightly higher risk of hospitalization postvaccination

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ABSTRACT

This study explores adverse events severe enough to warrant hospitalization that may have been associated with receiving the smallpox vaccine in conjunction with military service. Cox proportional hazards modeling was used to identify the risk of hospitalization among US active-duty military personnel during a 1-year period following receipt of the smallpox vaccine. The reference group consisted of active-duty military personnel who also received the smallpox vaccine after the conclusion of their health care observation period, allowing for comparison to a temporally and demographically similar population. The risk of hospitalization was slightly elevated among the postvaccine group for any-cause hospitalization and for hospitalization in several broad diagnostic categories. Hospitalizations for asthma, autoimmune diseases, and myopericarditis, were more likely in the postvaccine group. The increased risk of hospitalization for varied outcomes does not necessarily imply a cause–effect relationship, but it does offer areas for more focused study, using longitudinal data to explore the long-term impact of smallpox vaccination on the health of young adults.

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1. Introduction

Through extensive vaccination efforts [1], smallpox was globally eradicated in 1977. Easily transmitted from person to person, with approximately 30 percent of all cases being fatal, there is growing concern that smallpox may return through biological weaponization [2,3]. In response to perceived threats of biological weapons use, the US Department of Defense (DoD) established the Smallpox Vaccination Program for selected military personnel on December 13, 2002, and vaccinated more than one million service personnel as of May 2007 [4].

Smallpox vaccine has been administered to millions of individuals and many short-term adverse health effects associated with smallpox vaccination have been documented from earlier investigations and more recent Department of Health and Human Services investigations [5,6]. Cases of myopericarditis and other cardiac disease occurring within 6 weeks of vaccination [7–9] and of dilated cardiomyopathy identified within 5–29 weeks after vaccination [10] have been of concern [5,11,12]. The DoD, in conjunction with the Centers for Disease Control and Prevention and the US Food

and Drug Administration, continues to monitor short-term adverse events associated with the administration of vaccines through the Vaccine Adverse Events Reporting System (VAERS) [13]. Although VAERS data are useful in signaling potential new adverse events, this passive surveillance system has limitations [14,15]. With continued concerns over smallpox vaccine safety [16,17], it is important to conduct further studies regarding broad health outcomes in smallpox vaccine recipients over a longer period of time. The purpose of this study was to explore the health of individuals receiving the smallpox vaccine by examining hospitalization experiences up to 1 year after vaccination.

2. Methods

2.1. Data

Smallpox immunization data for calendar years 2003 and 2004 were extracted from the Defense Enrollment Eligibility Reporting System at the Defense Manpower Data Center (DMDC), Monterey Bay, CA. Demographic data were obtained from DMDC and hospitalization data were obtained from the Standard Inpatient Data Record and the Health Care Service Record, representing all inpatient care at civilian and military facilities for active-duty members. Hospital discharge diagnoses were identified using *International*

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Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM) codes. All files were obtained in electronic format and were linked by personal identifiers.

2.2. Study population

Individuals who received a smallpox vaccination between January 1, 2003, and December 31, 2004, served on continuous active duty for 12 months prior to their vaccination date, and had complete demographic data were included in this analysis. Those who had any deployment in support of the Global War on Terror (GWOT) during the year prior to vaccination and those who deployed to GWOT within 60 days of receiving the vaccine were excluded from the analysis. These criteria were imposed due to the differential visibility of hospitalization data during deployment as well as differences in access to care among active-duty and Reserve/National Guard service members. All subjects ultimately received the smallpox vaccine, and therefore, the exposure group of interest was called the "postvaccine" group, and the reference group was called "reference." Postvaccine subjects received a smallpox vaccination between the period of January 1 and June 30, 2003 or 2004 and were observed for hospitalization encounters *after* their vaccination date. Reference subjects received a smallpox vaccination between July 1 and December 31 of the same years (2003 or 2004), but they were observed for hospitalization encounters *before* their vaccination date. The use of this novel reference group maximized similarities with the postvaccine group, since both populations were eligible for vaccination. In addition, this methodology provided overlapping observation windows to reduce any systematic bias that may have occurred with the administration of the smallpox vaccine or hospitalization procedures during a certain time period.

2.3. Outcomes

This study aimed to identify severe health effects, excluding mortality and pregnancy-related outcomes, associated with smallpox vaccination during a 1-year period following vaccination. Outcomes requiring hospitalization were analyzed to focus on severe health issues. Outcomes included hospitalization for any cause and hospitalizations among 14 broad ICD-9-CM categories [18]. To understand which diagnoses were driving the significance of a major diagnostic category, the five most frequently reported 3-digit codes within each significant category were identified and then examined individually. Hospitalizations for certain autoimmune diseases and asthma were also examined.

Autoimmune diseases were defined using the Johns Hopkins Autoimmune Disease Research Center Web site [19] as a primary source. This source was verified against three other sources as follows: Harrison's Principles of Internal Medicine [20], the American Autoimmune Related Diseases Association Web site [21], and the National Library of Medicine Lab Tests Online Web site [22]. After reconciling these lists, a group of clinicians then assigned ICD-9-CM codes for the disorders based on their clinical knowledge. Because of the rarity of many of these conditions, all autoimmune diseases were investigated in the aggregate.

Based on prior reports of smallpox vaccine-related myopericarditis [11,23,24], these analyses examined this diagnosis using several different definitions. The first definition used specific criteria (ICD-9-CM codes 420.9x, 422.90, 422.91, 422.99, 429.0). The second definition included the codes from the first and also added adhesive pericarditis (423.1), constrictive pericarditis (423.2), unspecified diseases of pericardium (423.9), myocarditis unspecified (429.0), and heart disease unspecified (429.9). The third definition included the first two and also added chest pain

(786.5x). The broadest diagnostic criteria encompassed the codes from the first three definitions, and added conduction disorders (426.xx) and cardiac dysrhythmias (427.xx) that could have been due to myopericarditis.

2.4. Statistical analyses

Pearson chi-square tests were used to examine the univariate measures of association between any-cause hospitalization and vaccination status, demographic, and military variables. Exploratory analyses were conducted to assess significant associations and possible confounding while adjusting for other variables in the model. Collinearity among the independent variables was also examined using regression diagnostics. Cox proportional hazards time-to-event modeling was used to compare hospitalizations among the postvaccine and reference group. Subjects who experienced a hospitalization during the follow-up period for any cause among the 14 broad ICD-9-CM categories were classified as having an event. Follow-up time for the postvaccine group began at the day of smallpox vaccination and continued until an individual experienced an event, which included hospitalization, deployment, or separation from military service. If no event was experienced, the duration of the follow-up period was 1 year. Follow-up time for the reference group began 1-year prior to the date of smallpox vaccination and continued until an individual experienced a hospitalization. If no hospitalization was experienced, the duration of the follow-up period was 1 year. Because the individuals in the reference group were serving on active-duty military service at the time of vaccination, they were excluded from the study if they either deployed or separated from military service during their follow-up (prevaccination) period. Adjusted hazard ratios and 95 percent confidence intervals were calculated for all outcomes.

To understand whether the relationship between vaccination status and any-cause hospitalization, asthma, autoimmune disorders, and myopericarditis was being modified by gender, an interaction term was included in each of these models. Interaction terms were considered significant at $\alpha = 0.10$ level.

In addition, clustering of cases over time during the health care observation period was investigated. Among the postvaccine group, the 1-year follow-up period was divided into five groups: 0–30 days, 31–60 days, 61–90 days, 91–120 days, and >120 days. For each diagnosis that was significantly associated with vaccination status, the proportion of cases diagnosed within each time period was examined to evaluate the temporal relationship between vaccination and hospitalization.

3. Results

Of the more than 800,000 service members who received a smallpox vaccine in 2003 or 2004, 425,297 individuals served on continuous active duty for 12 months prior to their vaccination date and had complete demographic data. Of these individuals, 122,502 did not have any deployments in support of GWOT during the year prior to their vaccination, nor did they deploy to GWOT within 60 days of receiving their vaccination. The postvaccine group consisted of a greater proportion of older, Navy and Marine Corps, health care specialists, and married personnel when compared to the reference (Table 1).

Cox proportional hazards time-to-event modeling was employed to examine the risk of hospitalization for any cause (Table 2). Gender did not significantly modify the relationship between any-cause hospitalization, asthma, myopericarditis, or autoimmune diseases and vaccination status, so stratified analyses were not performed. Those with increased adjusted risk for

Table 1Characteristics of 2003 and 2004 smallpox-vaccinated^a service members and 2003 total active-duty military

Characteristic ^b	Postvaccine ^c n = 80,214 (n (%))	Reference ^c n = 42,288 (n (%))	Active-duty military, 2003 ^d n = 1,318,423 (n (%))
Gender			
Male	68,605 (85.5)	36,202 (85.6)	1,126,013 (85.4)
Female	11,609 (14.5)	6,086 (14.4)	192,410 (14.6)
Age group (years)			
≤24	37,002 (46.1)	22,890 (54.1)	597,288 (45.3)
25–34	26,413 (32.9)	12,200 (28.9)	411,119 (31.2)
≥35	16,799 (21.0)	7,198 (17.0)	310,016 (23.5)
Race/ethnicity			
White, non-Hispanic	49,242 (61.4)	25,824 (61.1)	841,823 (63.9)
Black, non-Hispanic	17,684 (22.0)	9,138 (21.6)	266,516 (20.2)
Hispanic	8,315 (10.4)	4,324 (10.2)	126,655 (9.6)
Other	4,973 (6.2)	3,002 (7.1)	83,429 (6.3)
Highest educational level			
High school, or less	67,925 (84.7)	35,621 (84.2)	1,096,057 (83.1)
Some college	3,962 (4.9)	2,591 (6.1)	73,353 (5.6)
Bachelor's degree or higher	8,327 (10.4)	4,076 (9.7)	149,013 (11.3)
Rank			
Officer	6,111 (7.6)	2,494 (5.9)	113,057 (8.6)
Enlisted	74,103 (92.4)	39,794 (94.1)	1,205,366 (91.4)
Service branch			
Army	52,007 (64.9)	26,968 (63.8)	451,386 (34.2)
Air Force	13,329 (16.6)	10,294 (24.3)	329,808 (25.0)
Navy	8,362 (10.4)	2,670 (6.3)	356,246 (27.0)
Marine Corps	6,516 (8.1)	2,356 (5.6)	180,983 (13.7)
Occupational codes			
Combat specialists	19,931 (24.8)	9,319 (22.1)	273,713 (20.8)
Electrical/mechanical equipment repair	12,487 (15.6)	7,796 (18.4)	240,330 (18.2)
Functional support and administration	9,833 (12.3)	6,864 (16.2)	216,062 (16.4)
Service and supply	8,012 (10.0)	4,252 (10.1)	119,331 (9.0)
Communications/intelligence	6,964 (8.7)	4,206 (10.0)	116,112 (8.8)
Health care	12,433 (15.5)	3,429 (8.1)	91,761 (7.0)
Electronic repair	5,495 (6.8)	3,539 (8.4)	121,174 (9.2)
Craft workers	1,729 (2.2)	992 (2.3)	41,178 (3.1)
Other technical and specialty	2,257 (2.8)	1,325 (3.1)	35,993 (2.7)
Students, trainees, others	1,073 (1.3)	566 (1.3)	62,769 (4.8)
Marital status			
Married	41,601 (51.9)	20,345 (48.1)	683,205 (51.8)
Single	35,238 (43.9)	19,955 (47.2)	590,294 (44.8)
Other	3,375 (4.2)	1,988 (4.7)	44,924 (3.4)
Pre-study observation hospitalization status ^e			
Not hospitalized	76,997 (96.0)	40,870 (96.7)	
Hospitalized	3,217 (4.0)	1,418 (3.3)	

^a Service members included in this study received their primary smallpox vaccine between January 1, 2003, and December 31, 2004, served on active duty for 12 continuous months prior to their vaccination date, and had complete covariate data.

^b Chi-square tests of significance were calculated between the vaccination group variable and all independent variables that appear in the table. All chi-square tests of significance, except gender, were statistically significant at $p < 0.05$.

^c Military personnel in the postvaccine group received the smallpox vaccine between January 1 and June 30 of 2003 or 2004, and their hospitalizations were observed for a 1-year period after their vaccination date. Military personnel in the reference group received the smallpox vaccine between July 1 and December 31 of 2003 or 2004, and their hospitalizations were observed for a 1-year period prior to their vaccination date.

^d Force on active-duty rosters as of July 2003.

^e Prevaccination hospitalization status indicates if a participant was hospitalized for any reason during the year immediately prior to the study observation period.

hospitalization included individuals in the postvaccine group (hazard ratio [HR]: 1.12; 95 percent confidence interval [CI]: 1.04, 1.20), women (HR = 1.43; 95 percent CI: 1.31, 1.57), those >34 years of age (HR = 1.25; 95 percent CI: 1.11, 1.39), enlisted personnel (HR = 1.46; 95 percent CI: 1.18, 1.81), and those employed in the health care field (HR = 1.25; 95 percent CI: 1.12, 1.40).

A significantly increased adjusted risk of hospitalization after smallpox vaccination was observed in six of the 14 broad ICD-9-CM diagnostic categories: endocrine and metabolic disorders, mental disorders, diseases of the circulatory system, diseases of the blood, nervous system disorders, and symptoms, signs, and ill-defined conditions (Fig. 1). Adjusted risk of hospitalization among the eight

other categories was not significantly associated with vaccination status.

The five most frequent diagnoses within each broad, significant ICD-9-CM category were examined (Table 3). Within the endocrine and metabolic category, the adjusted risk of hospitalization for disorders of lipid metabolism was 2.43 times greater for the post-vaccine group than for those in the reference group (95 percent CI: 1.42, 4.18). A significantly increased adjusted risk of hospitalization existed for four of the most common diagnoses within the mental disorders category, most notably the more than two-fold increased risk of hospitalization for affective psychoses (95 percent CI: 1.42, 3.45). There was a two-fold increased adjusted

Table 2

Characteristics and risk of any-cause hospitalization for active-duty service members receiving the smallpox vaccine between January 1, 2003, and December 31, 2004

Characteristic	Hospitalized n = 3521 (n (%))	Not hospitalized n = 118,981 (n (%))	HR ^a	95% CI ^a	p Value
Exposure to smallpox vaccine ^b					<0.01
Reference	1,392 (39.5)	40,896 (34.4)	1.00		
Postvaccine	2,129 (60.5)	78,085 (65.6)	1.12	1.04, 1.20	
Gender					<0.01
Male	2,775 (78.8)	102,032 (85.8)	1.00		
Female	746 (21.2)	16,949 (14.2)	1.43	1.31, 1.57	
Age group (years)					<0.01
≤24	1,723 (48.9)	58,169 (48.9)	1.00		
25–34	1,047 (29.8)	37,566 (31.6)	0.97	0.89, 1.06	
≥35	751 (21.3)	23,246 (19.5)	1.25	1.11, 1.39	
Race/ethnicity					<0.01
White, non-Hispanic	2,143 (60.9)	72,923 (61.3)	1.00		
Black, non-Hispanic	819 (23.2)	26,003 (21.9)	0.91	0.84, 0.99	
Hispanic	355 (10.1)	12,284 (10.3)	0.90	0.80, 1.01	
Other	204 (5.8)	7,771 (6.5)	0.81	0.70, 0.94	
Highest educational level					0.38
High school, or less	3,016 (85.6)	100,530 (84.5)	1.00		
Some college	189 (5.4)	6,364 (5.3)	0.93	0.80, 1.09	
Bachelor's degree or higher	316 (9.0)	12,087 (10.2)	0.90	0.76, 1.07	
Rank					<0.01
Officer	1,964 (5.5)	8,411 (7.1)	1.00		
Enlisted	3,327 (94.5)	110,570 (92.9)	1.46	1.18, 1.81	
Service branch					<0.01
Army	2,578 (73.2)	76,397 (64.2)	1.00		
Air Force	496 (14.1)	23,127 (19.4)	0.53	0.48, 0.58	
Navy	258 (7.3)	10,774 (9.1)	0.58	0.51, 0.66	
Marine Corps	189 (5.4)	8,683 (7.3)	0.72	0.62, 0.84	
Occupational codes					<0.01
Combat specialists	789 (22.4)	28,461 (23.9)	1.00		
Electrical/mechanical equip. repair	554 (15.7)	19,729 (16.6)	1.01	0.90, 1.13	
Functional support and admin	459 (13.0)	16,238 (13.6)	0.88	0.78, 1.00	
Service and supply	410 (11.7)	11,854 (10.0)	1.11	0.98, 1.25	
Communications/intelligence	267 (7.6)	10,903 (9.2)	0.85	0.74, 0.98	
Health care	638 (18.1)	15,224 (12.8)	1.25	1.12, 1.40	
Electronic repair	219 (6.2)	8,815 (7.4)	0.92	0.79, 1.07	
Craft workers	56 (1.6)	2,665 (2.2)	0.85	0.64, 1.11	
Other technical and specialty	95 (2.7)	3,487 (2.9)	0.94	0.76, 1.17	
Students, trainees, others	34 (1.0)	1,605 (1.4)	0.77	0.54, 1.08	
Marital status					0.61
Married	1,754 (49.8)	60,192 (50.6)	1.00		
Single	1,591 (45.2)	53,602 (45.0)	1.04	0.96, 1.13	
Other	176 (5.0)	5,187 (4.4)	1.04	0.88, 1.21	
Pre-study observation hospitalization status ^c					<0.01
Not hospitalized	3,194 (90.7)	114,673 (96.4)	1.00		
Hospitalized	327 (9.3)	4,308 (3.6)	2.39	2.13, 2.69	

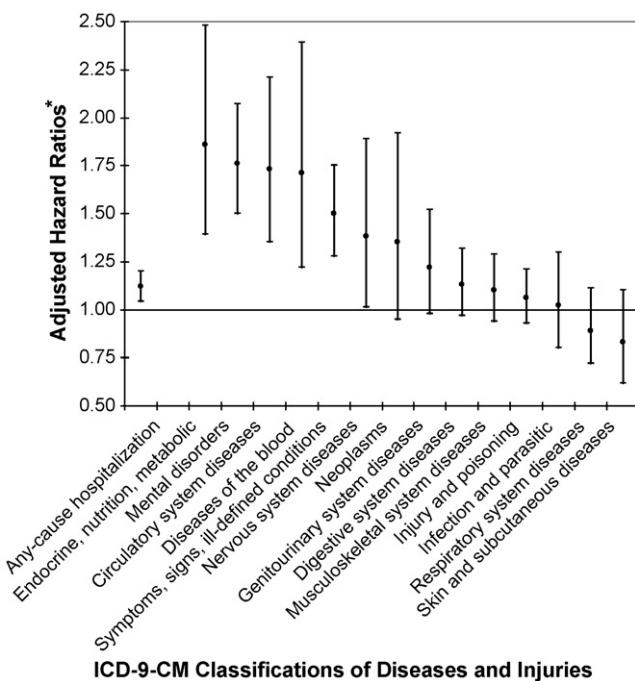
^a Hazard ratio (HR) and 95% confidence interval (CI) were adjusted for all other variables listed in the table.^b Military personnel in the postvaccine group received the smallpox vaccine between January 1 and June 30 of 2003 or 2004, and their hospitalizations were observed for a 1-year period after their vaccination date. Military personnel in the reference group received the smallpox vaccine between July 1 and December 31 of 2003 or 2004, and their hospitalizations were observed for a 1-year period prior to their vaccination date.^c Prevaccination hospitalization status indicates if a participant was hospitalized for any reason during the year immediately prior to the study observation period.

risk of hospitalization for other and unspecified anemias (95 percent CI: 1.33, 3.35) within the category for diseases of the blood. An almost two-fold increased adjusted risk for hospitalization for symptoms involving the respiratory system and "other ill-defined and unknown causes for morbidity and mortality" existed within the category of symptoms, signs, and ill-defined conditions. Conditions significantly associated with vaccination were proportionally distributed throughout the observation period, except for the category of other ill-defined and unknown causes of morbidity and mortality, of which 26.5 percent of cases appeared in the first 30 days after vaccination (data not shown).

Asthma and autoimmune diseases were separately examined. Those in the postvaccine group were 2.24 times more likely to

be hospitalized for asthma (95 percent CI: 1.21, 4.17) and 2.77 times more likely to be hospitalized for autoimmune diseases (95 percent CI: 1.19, 6.46) than subjects in the reference group. The most frequent diagnoses, accounting for approximately 40% of the autoimmune diseases, were inflammatory bowel diseases.

The authors examined myopericarditis using several different definitions, ranging from specific to sensitive (see Table 4). Using the most specific definition for myopericarditis, only 23 cases were identified. Those in the postvaccine group were 2.33 times more likely to be hospitalized than those in the reference group, although this relationship was not statistically significant (95 percent CI: 0.85, 6.43). As the myopericarditis definitions became more sensitive, more cases were identified, the hazard ratios decreased



ICD-9-CM Classifications of Diseases and Injuries

Fig. 1. Adjusted hazard of hospitalization among active-duty smallpox vaccinated service members, 2003–2004. Adjusted hazard ratios and 95% confidence intervals for first hospitalization after smallpox vaccination were adjusted for gender, age, education, marital status, race/ethnicity, pay grade, branch of service, and occupation.

slightly, and the confidence intervals narrowed and became statistically significant. Using the most sensitive definition, 228 cases were identified, and those in the postvaccine group were 1.85 times more likely to be hospitalized than the reference group (95 percent CI: 1.36, 2.50). The greatest proportion of myopericarditis cases occurred within the first 30 days after vaccination, though the proportion of cases in the first 30 days decreased as the definition became more sensitive (data not shown).

4. Discussion

In this investigation, we observed a marginally significant increased risk for any-cause hospitalization for those in the post-smallpox vaccine group compared with the reference group. The increased risk for any-cause hospitalization among women, older age groups, White, non-Hispanics, and health care workers may simply reflect trends seen in the general population, and has been reported in another study on postvaccination hospitalization [25], as well as in a study on health care utilization in a military population [26]. While the authors are not aware of a known association between White, non-Hispanic race and vulnerability to adverse events after smallpox vaccine, this relationship has been described in a previous study examining myopericarditis [27] after smallpox vaccine, and perhaps warrants further study. We also found an increased risk for hospitalization for any cause among enlisted and Army personnel. If enlisted status is considered a surrogate for socioeconomic status, then a higher rate of hospitalization among this group is not surprising. The increased risk of hospitalization among Army personnel is not easily explained, although it has been found in other studies [25,26], and may be due to procedural differences in reporting, or policies regarding the use of inpatient versus outpatient care among the services. In addition, postvaccine subjects were significantly more likely to be hospitalized for diagnoses in 6 of the 14 broad ICD-9-CM diagnostic categories, including

endocrine and metabolic diseases, mental disorders, circulatory system diseases, diseases of the blood, diseases of the nervous system, and signs, symptoms, and ill-defined conditions. This study also revealed an association between smallpox vaccination status and hospitalization for myopericarditis, asthma, and autoimmune diseases.

Epidemiological studies of vaccine-related adverse effects can be challenging. Randomized, double-blind, placebo-controlled trials are generally not possible in the post-marketing phase to examine rare adverse events [28,29], thereby necessitating observational studies. When studying the long-term health effects of a vaccine such as smallpox [30,31], the task of selecting the best reference group for an observational study is especially challenging. Other epidemiologic vaccine studies in military populations have confronted the same issue of selecting an appropriate reference group. Therefore, many studies investigating the adverse health effects of the smallpox vaccine have used surveillance monitoring or case reports [24,32–34], lacking the ability to make comparisons to other populations. Past work researching the morbidity associated with smallpox and anthrax vaccines compared vaccinated and unvaccinated individuals [35–37], or used the same group of people and compared them pre- and postvaccination [25], with no significantly increased risk of hospitalization among the immunized discovered in any of these studies.

In this study, we examined the risk of hospitalization after smallpox vaccination by comparing this risk with that of another group who were eligible for smallpox vaccine, by evidence of their future vaccination. This design allowed for subjects to share many of the same demographic and military characteristics, including potential to deploy, as well as other metrics that may be temporally associated with hospitalization. Selecting this comparison group minimized the potential “healthy worker effect” [38] that may be inherent when comparing workers who are eligible for vaccinations with those who are ineligible. While the current study showed only a slight elevated risk of hospitalization among the smallpox immunized, perhaps using a reference group with such similar demographic and exposure characteristics allowed for the detection of small differences between groups.

We conducted a more thorough examination of the elevated risk for hospitalization among health care workers. Health care workers and first responders were among the earliest to be vaccinated, which is evident with nearly twice as many health care workers in the postvaccine group than the reference group. Health care workers may utilize health care services at a higher rate, and this may influence the findings of the current study, even after mathematical adjustment in the multivariable models. Therefore, we explored the any-cause hospitalization model after excluding health care workers. The risk of any-cause hospitalization remained consistent in magnitude and significance, suggesting these differences could not be attributed to the greater proportion of health care workers in the postvaccine group.

When examining the five most frequent diagnoses within broad ICD-9-CM categories, several specific diagnoses were associated with smallpox vaccination status, including several mental disorders, disorders of lipid metabolism, and other and unspecified anemias. These findings are not easily explained, have not been reported in previous literature, and may have been due to multiple comparison or confounding issues. Investigation of the temporal proximity of diagnosis to vaccination date did not help to explain these statistically significant findings. The relatively random distribution of cases over time after vaccination indicated that no temporal relationship between vaccination and hospitalization exists for these conditions. Nonetheless, further exploration of these relationships may be warranted, as biological plausibility may indeed exist for mental disorders such as psychoses.

Table 3

Frequencies and adjusted hazard ratios of the five most common diagnoses among the broad ICD-9-CM diagnostic categories significantly associated with hospitalization, by smallpox vaccination timing

ICD-9-CM category ^a	Diagnoses	Frequency of diagnoses				HR ^b	95% CI ^b		
		Postvaccine ^c (n = 80,214)		Reference ^c (n = 42,288)					
		n	%	n	%				
Endocrine, nutritional and metabolic diseases and disorders (codes 240–279)									
276	Disorders of fluid, electrolyte, and acid–base balance	65	0.1	39	0.1	1.15	0.76, 1.73		
272	Disorders of lipid metabolism	74	0.1	17	0.0	2.43	1.42, 4.18		
250	Diabetes mellitus	23	0.0	2	0.0				
244	Acquired hypothyroidism	19	0.0	2	0.0				
278	Obesity and other hyperalimentation	17	0.0	3	0.0				
Mental disorders (codes 290–319)									
305	Nondependent abuse of drugs	195	0.2	99	0.2	1.61	1.26, 2.06		
309	Adjustment reaction	156	0.2	69	0.2	1.95	1.46, 2.61		
296	Affective psychoses	77	0.1	28	0.1	2.21	1.42, 3.45		
300	Depressive disorder, not elsewhere classified	60	0.1	32	0.1	1.27	0.81, 1.99		
311	Neurotic disorders	61	0.1	24	0.1	1.94	1.19, 3.15		
Diseases of the circulatory system (codes 390–459)									
401	Essential hypertension	102	0.1	27	0.1	2.37	1.53, 3.66		
427	Cardiac dysrhythmias	38	0.0	19	0.0	1.28	0.72, 2.27		
411	Other acute and subacute form of ischemic heart disease	20	0.0	5	0.0	2.27	0.83, 6.19		
414	Other forms of chronic ischemic heart disease	18	0.0	4	0.0				
415	Acute pulmonary heart disease	15	0.0	3	0.0				
Disease of the blood and blood forming organs (codes 280–289)									
285	Other and unspecified anemias	69	0.1	26	0.1	2.11	1.33, 3.35		
287	Purpura and other hemorrhagic conditions	18	0.0	7	0.0	1.92	0.79, 4.69		
280	Iron deficiency anemias	16	0.0	7	0.0	1.52	0.60, 3.84		
288	Diseases of white blood cells	11	0.0	6	0.0	1.43	0.51, 3.97		
289	Other diseases of blood and blood forming organs	8	0.0	3	0.0				
Symptoms, signs, and ill-defined conditions (codes 780–799)									
780	General symptoms	103	0.1	75	0.2	1.02	0.75, 1.39		
786	Symptoms involving respiratory system and other chest symptoms	132	0.2	44	0.1	1.97	1.39, 2.79		
789	Other symptoms involving abdomen and pelvis	71	0.1	43	0.1	1.18	0.79, 1.74		
799	Other ill-defined and unknown causes of morbidity and mortality	68	0.1	28	0.1	1.84	1.18, 2.88		
784	Symptoms involving head and neck	36	0.0	22	0.1	1.09	0.63, 1.90		
Diseases of the nervous system and sense organs (codes 320–389)									
346	Migraine	25	0.0	12	0.0	1.31	0.64, 2.67		
348	Other conditions of the brain	10	0.0	4	0.0				
354	Mononeuritis of upper limb and mononeuritis multiplex	10	0.0	3	0.0				
349	Other and unspecified disorders of the nervous system	8	0.0	4	0.0				
368	Visual disturbances	7	0.0	3	0.0				

^a ICD-9-CM, *International Classification of Diseases*, Ninth Revision, Clinical Modification.

^b Hazard ratio (HR) and associated 95% confidence interval (CI) from multiple logistic regression were adjusted for gender, age, education, marital status, race/ethnicity, military rank, branch of service, and occupation. HR and associated 95% CI were not calculated for cell sizes with fewer than five observations.

^c Military personnel in the postvaccine group received the smallpox vaccine between January 1 and June 30 of 2003 or 2004, and their hospitalizations were observed for a 1-year period after their vaccination date. Military personnel in the reference group received the smallpox vaccine between July 1 and December 31 of 2003 or 2004, and their hospitalizations were observed for a 1-year period prior to their vaccination date.

Table 4

Adjusted hazard ratios for hospitalization for specific diagnoses of interest, by smallpox vaccination timing

Diagnosis (ICD-9-CM codes) ^a	Cases				HR (95% CI) ^b	
	Postvaccine ^c (n = 80,214)		Reference ^c (n = 42,288)			
	n	%	n	%		
Myopericarditis specific codes (420.9x, 422.90, 422.91, 422.99, 429.0)						
Myopericarditis broader code set (420.9x, 420, 422, 422.9, 422.90, 422.91, 422.99, 423.1, 423.2, 423.9, 429.0, 429.9)	18	(0.0)	5	(0.0)	2.33	0.85, 6.43
Myopericarditis broader, more sensitive code set (420.9x, 420, 422, 422.9, 422.90, 422.91, 422.99, 423.1, 423.2, 423.9, 429.0, 429.9, 786.5x)	25	(0.0)	8	(0.0)	2.15	0.95, 4.86
Myopericarditis broadest, most sensitive code set (420.9x, 420, 422, 422.9, 422.90, 422.91, 422.99, 423.1, 423.2, 423.9, 429.0, 429.9, 786.5x, 426.xx, 427.xx)	130	(0.2)	40	(0.1)	2.10	1.46, 3.03
Myopericarditis broadest, most sensitive code set (420.9x, 420, 422, 422.9, 422.90, 422.91, 422.99, 423.1, 423.2, 423.9, 429.0, 429.9, 786.5x, 426.xx, 427.xx)	169	(0.2)	59	(0.1)	1.85	1.36, 2.50

^a Diagnoses and codes were from the ICD-9-CM, *International Classification of Diseases*, Ninth Revision, Clinical Modification.

^b Hazard ratio (HR) and 95% confidence interval (CI) were adjusted for gender, age, race/ethnicity, education, marital status, military rank, military service branch, and military occupation.

^c Military personnel in the postvaccine group received the smallpox vaccine between January 1 and June 30 of 2003 or 2004, and their hospitalizations were observed for a 1-year period after their vaccination date. Military personnel in the reference group received the smallpox vaccine between July 1 and December 31 of 2003 or 2004, and their hospitalizations were observed for a 1-year period prior to their vaccination date.

The authors found the elevated risk for hospitalization for essential hypertension after smallpox vaccine interesting. Although adverse event monitoring for smallpox vaccine in 2003 revealed several hypertensive episodes among cardiac events, of which inflammatory processes may play a part, a causal link between smallpox vaccine and such cardiac events remains unclear [9,24]. Further exploration of the relationship between vaccination and hypertension may also be warranted.

Consistent with past research, we found a significant increased risk of hospitalization for myopericarditis after smallpox vaccination [5,7,11,32]. The risk of hospitalization for myopericarditis decreased slightly as the definition became more sensitive and more cases were identified, however, the significance of the relationship strengthened (see Table 4). This decrease in strength of the association with an increase in the significance of the relationship likely reflected the growing number of cases identified as the definitions became more sensitive. In addition, the strong clustering of myopericarditis cases within the first 30 days after vaccination indicated that this condition was temporally associated with receipt of the smallpox vaccine. Because myopericarditis may be diagnosed only as nonspecified chest pain, we found it important to examine a more sensitive definition to capture all possible cases. When considering the hazard ratios for each of the definitions investigated, the risk for hospitalization due to myopericarditis after smallpox vaccine may have been twice that of the referent group. To our knowledge, this is the first population-based quantification of the previously identified risk of myopericarditis after smallpox vaccination.

The authors also found that individuals in the postvaccine group had more than twice the risk of hospitalization for asthma and autoimmune diseases than did the reference group. The number of cases was small, and the confidence intervals surrounding the measures of association lacked precision. These findings deserve further exploration, since other research has suggested that the association between autoimmune diseases and vaccines is biologically plausible [39–41]. In addition, the death of a young Army recruit in 2003 after receiving five simultaneous vaccinations, including smallpox and anthrax, may have been related to an autoimmune condition that may have been caused by the vaccinations [42]. However, in contrast to other diagnoses, the design of this study makes a causal association between these diagnoses and vaccination less likely. This is because preexisting asthma or autoimmune disease may have made service members relatively ineligible to be vaccinated. The reference group was a prevaccine group and therefore inherently less likely to be hospitalized for these conditions. This again highlights the challenges of selecting an appropriate reference population for all conditions of interest.

There are several limitations of this study that should be noted. First, these analyses were limited to hospital discharge data. Although hospitalization data identify more severe morbidity and are very complete while service members are on active duty, potentially interesting but less severe events were not captured by this study. Furthermore, there is no hospitalization assessment once the member leaves the military. However, this analysis complements an analysis that did evaluate less severe morbidities using the Millennium Cohort Study [43] to assess self-reported adverse health outcomes related to smallpox vaccination [44]. The current study was subject to potential misclassification bias due to the use of hospital discharge data. Diagnostic coding challenges would have most affected rare conditions and those difficult to diagnose, potentially causing differential reporting of some diagnoses. An extremely important limitation of this study was the inability to adjust for other types of vaccines given simultaneously with the smallpox vaccine. Many individuals who received the smallpox vaccine were likely to receive the anthrax vaccine and/or other

immunizations simultaneously, in accordance with current military policy [10,45]. Therefore, the authors were not able to know whether the observed effects and elevated risks among certain subgroups were attributable to receipt of the smallpox vaccine, or to the receipt of several different vaccines concurrently. Research is ongoing to investigate the role of multiple occupationally related vaccines administered concurrently.

Sampling limitations for this study should be noted. Some bias in selection of the reference group for healthy individuals may have occurred since service members are less likely to be immunized if they have any autoimmune disorders prior to vaccination [46]. Additionally, the authors were not able to distinguish between those receiving a primary or secondary smallpox vaccine. Because subjects in the postvaccine group were older than those in the reference group, the postvaccine group was more likely to contain individuals who received a secondary vaccination. Therefore the observed effects of smallpox vaccination may have been diluted because individuals receiving a primary vaccination have been shown to have more severe adverse events compared to those receiving a secondary vaccine [47]. Moreover, because hospitalization data were not available for service members who deployed or were no longer on active duty, these analyses were restricted to active-duty populations prior to deployment, possibly biasing the sample. The study population was also limited to individuals with 1 year of continuous service prior to their vaccination date, thereby excluding a large proportion of smallpox-vaccinated individuals who may have enlisted and deployed quickly, receiving the vaccine just prior to deployment. In addition, those who deployed within 60 days of receiving the vaccine were excluded in order to have sufficient follow-up time for the postvaccine group, which may have created a bias since individuals may deploy shortly after smallpox vaccination to avoid household contacts. Because the postvaccine subjects were followed for 1 year after their vaccination date until hospitalization, deployment, or separation, any hospitalizations that may have occurred after these events would have been missed. This may have limited our ability to detect diseases with a longer latency period. Additionally, individuals who separate from the military may have higher hospitalization rates because they undergo thorough medical examinations before separation, or morbidity may be the catalyst for their separation. Therefore, because the study design did not permit individuals in the reference group to separate during the observation period, this may have contributed to a lower hospitalization rate among the reference group. Lastly, due to the exploratory nature of this investigation, no adjustments for multiple comparisons were made. With the many models investigated in these analyses, it is possible that some of the significant findings were spurious.

Despite these limitations, several strengths should be noted. The robust size of the sample allowed sufficient power to examine the association between smallpox vaccination and specific diagnoses, except those with a low rate of hospitalization. Also, hospitalization data may be more objective and/or accurate measures of morbidity, in comparison with ambulatory data or self-reported data. Additionally, these data were from DoD hospitals worldwide along with civilian hospitals billing to the DoD, and the data are considered very complete. Moreover, active-duty military personnel are assumed to have equal access to care. The use of a reference group that was vaccinated after the health care observation period allowed for a militarily and demographically similar comparison group and minimized some of the potential "healthy worker effect" biases. In addition, the use of Cox proportional hazards modeling accounted and adjusted for the length of time contributed by each member of the study.

In conclusion, this study examined the risk of hospitalization among individuals after smallpox vaccine by using a novel

reference group that was also vaccinated against smallpox in the future and was demographically similar to the postvaccine population. Smallpox vaccination was significantly associated with a slightly increased risk for any-cause hospitalization, and hospitalization in several diagnostic categories. While increased risk of hospitalization among the postvaccine group for a few conditions within the broad categories was biologically plausible, others, such as those in the mental disorders category, were unlikely related to smallpox vaccine. The elevated risk for hospitalization due to broadly defined myopericarditis after smallpox vaccine quantified and supported a relationship that had previously been observed [5,7,11,32]. These findings should be viewed as a complement to a growing portfolio of research enhancing understanding of relatively common, but important, vaccine-related health effects. Future studies should focus on addressing the issue of multiple vaccines, as data are lacking concerning the simultaneous administration of smallpox, anthrax, and other vaccines.

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14. ABSTRACT (maximum 200 words)

Since December 2002, the smallpox vaccine has been administered to more than one million military personnel perceived to be at risk of a possible biological warfare attack. This study explores adverse events severe enough to warrant hospitalization that may have been associated with receiving the smallpox vaccine. Cox proportional hazards modeling was used to identify the risk of hospitalization among active-duty military personnel during a 1-year period following receipt of the smallpox vaccine. This study used a novel reference group consisting of active-duty military personnel who also received the smallpox vaccine after the conclusion of their health care observation period, allowing for comparison with a temporally and demographically similar population. The risk of hospitalization was slightly elevated among the postvaccine group for all-cause hospitalization and for hospitalization in several broad diagnostic categories. Additionally, a significantly higher risk for asthma, autoimmune diseases, and myopericarditis, was detected after smallpox vaccination. The increased risk of hospitalization for varied outcomes does not necessarily imply a cause-and-effect relationship, but it does offer areas for more focused study. Additional research in this area using longitudinal data may be necessary to explore the long-term impact of smallpox vaccinations on the health of young adults.

15. SUBJECT TERMS

hospitalization, military medicine, smallpox vaccine, myopericarditis

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